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ECONOMIC EVALUATION AND THE POSTPONEMENT OF HEALTH CARE COSTS

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SUMMARY

The inclusion of medical costs in life years gained in economic evaluations of health care technologies has long been controversial. Arguments in favour of the inclusion of such costs are gaining support, which shifts the question from *whether* to *how* to include these costs. This paper elaborates on the issue how to include cost in life years gained in cost effectiveness analysis given the current practice of economic evaluations in which costs of related diseases are included. We combine insights from the theoretical literature on the inclusion of unrelated medical costs in life years gained with insights from the so-called ‘red herring’ literature. It is argued that for most interventions it would be incorrect to simply add all medical costs in life years gained to an ICER, *even* when these are corrected for postponement of the expensive last year of life. This is the case since some of the postponement mechanism is already captured in the unadjusted ICER by modelling the costs of related diseases. Using the example of smoking cessation, we illustrate the differences and similarities between different approaches. The paper concludes with a discussion about the proper way to account for medical costs in life years gained in economic evaluations. Copyright © 2010 John Wiley & Sons, Ltd.

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KEY WORDS: economic evaluation; medical costs in life years gained; modeling; cost effectiveness analysis

1. INTRODUCTION

When a successful intervention adds a few years to the life of some patient, this patient is bound to consume medical care during these years. Some of these costs may be directly related to the intervention. For instance, if the person had a life saving open heart surgery and would subsequently have to be treated for an infection of the wound on his chest, such costs are directly related to the surgery. Other costs, however, are unrelated to the intervention under study. For instance, if the same person while biking would fall due to a dog suddenly crossing the road and breaks a hip, the costs of treatment of the hip fracture are unrelated to the intervention. But still, without the successful heart surgery, obviously, the person would never have incurred these costs. The inclusion of these latter

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costs, the unrelated medical costs in life years gained, also called indirect medical costs, has long been controversial (Russell, 1986; Garber and Phelps, 1997; Meltzer, 1997; Weinstein and Manning, 1997; Nyman, 2004; van Baal *et al.*, 2007b; Meltzer, 2008; Lee, 2008; Feenstra *et al.*, 2008; Rappange *et al.*, 2008).

A first area of controversy relates to the definition of unrelated costs, which differs between the theoretical and the more practical literature on economic evaluations. In the theoretical debate, future unrelated medical costs are labelled as conditionally independent, implying that their height is not influenced by the intervention under study and depend, conditional on survival, exclusively on age (Garber and Phelps, 1997). It has been shown that inclusion of these conditionally independent costs is consistent with welfare maximization (Meltzer, 1997, 2008) and as long as the projections of length of added life and quality of life during added years (implicitly) assume normal care consumption, it would be inconsistent not to include the costs of such care (Nyman, 2004). Furthermore, including future medical costs as well as the health effects of that future medical spending results in ratios that are optimally informative for decision makers (van Baal *et al.*, 2007b). Only if an increase in the duration of life is accompanied by an increase in income, which covers all medical and non-medical expenses in added time, theoretically, a case could be made to exclude future unrelated medical costs, but this seems unrealistic to assume as a rule (Lee, 2008; Feenstra *et al.*, 2008; Rappange *et al.*, 2008). Concluding, there is growing consensus in the theoretical literature that future unrelated medical costs need to be included in cost effectiveness analyses. The obvious question then arises: how should we include them in practice? To answer this we have to understand how ageing of the population affects health care costs and what medical costs are usually included in economic evaluations.

In that context a second stream of literature, namely that on increases in health care costs due to ageing, is important. In recent years a lot of research has been performed studying the impact of ageing on health care expenditure from a macro perspective. In this area, an influential paper was published by (Zweifel *et al.*, 1999). They analysed the relationship between age and health care expenditure and found that health care expenditure depends importantly on proximity to death rather than age. Since higher average health care costs at older age are caused mainly by the fact that relatively many elderly people die, with associated intensive healthcare use and costs in the last period of life, they dubbed this the 'red herring' hypothesis (Seshamani and Gray, 2004a,b Hakkinen *et al.*, 2008; Spillman and Lubitz, 2000; Polder *et al.*, 2006). Obviously, these results have direct relevance for the question of how to include unrelated medical costs in added life years in economic evaluations. This was recognised by Gandjour and Lauterbach, who used these results to show that cost-effectiveness analyses potentially overestimate the incremental cost-effectiveness ratio (ICER) of preventive interventions when including unrelated medical costs in economic evaluations, if, in doing so, the high costs of the last year of life, which are postponed by prevention, are not explicitly modelled (Gandjour and Lauterbach, 2005). Using Medicare data they estimated that the cost-effectiveness ratio of preventive interventions may decrease up to US \$11 000. They do, however, make one important simplifying assumption in their analyses, i.e. that in economic evaluations (of preventive interventions) it is common practice to include *both* related and unrelated costs in life years gained and to model those costs exclusively depending on age.

However, here, the third relevant stream of literature comes into play, i.e. that regarding practical economic evaluations. Typically, as prescribed in many (pharmaco-economic) guidelines (e.g. CVZ, 2005; Gold *et al.*, 1996; NICE, 2008), cost-effectiveness analyses will only include related costs in life years gained while deliberately ignoring changes in unrelated costs altogether (e.g. Godfrey *et al.*, 2005; Mihaylova *et al.*, 2006). However, the costs that are termed 'related' and therefore included in practice do not necessarily adhere to the theoretical definitions of 'related'. In practice in economic evaluations related costs are usually defined on the level of diseases. Only the costs of diseases at which the intervention is targeted are taken into account. For instance, in an economic evaluation of statins for the treatment of cardiovascular disease, usually all costs of cardiovascular disease are labelled as related and included in the economic evaluation. For prevention aiming at risk factors, usually, costs of

diseases to which the risk factor is causally related are included. Thus, for a weight loss intervention, typically costs of diabetes and cardiovascular disease are included. The fact that *costs of related diseases* are not equivalent to *related costs* highlights a difference between the theoretical literature in this area and the practice of economic evaluations.

Given that costs of related diseases normally are already included in practical economic evaluations, it is incorrect to add all medical costs in life years gained to the ICER, even when corrected for the costs in the last year of life as suggested by Gandjour and Lauterbach, for two reasons: (i) the only costs that need to be added to the ICER in this context are the costs of unrelated diseases, since the costs of related diseases are already included and adding them again results in double-counting. Moreover, (ii) if the related costs are due to lethal diseases (i.e. diseases that influence survival), as they must when the intervention prolongs life, some of the postponement mechanism is already captured in the ICER. To illustrate the problem consider the following extreme example. Suppose that there exist only two diseases: one is lethal (e.g. cancer) and the other causes only a reduction in quality of life (e.g. osteoarthritis). Now suppose an intervention postpones the onset of cancer for five years, increasing life-expectancy from age 80 to 85 for people with osteoarthritis, and assume that the treatment costs of osteoarthritis increase with age. The intervention causes savings in the costs of cancer in normal years (the years lived up to the year of death at age 80) and additional costs in added years (years lived from 81 to age 85) for both cancer and osteoarthritis. Thus, the higher costs of the last year of life are postponed by the intervention. A standard economic evaluation would account for the related lifetime costs of cancer (which are postponed), but ignore the costs of osteoarthritis in life years gained. Then, obviously, adding the annual age-specific health care costs for the ages 80–85 would lead to double counting of costs of cancer. Moreover, applying the correction as proposed by Gandjour and Lauterbach in common economic evaluations, which include costs of related diseases, would also lead to incorrect adjustment of the ICER. Both the savings in normal life years and the costs in life years gained due to postponement of cancer are already taken into account. The only adjustment needed is the inclusion of osteoarthritis costs in life years gained and it suffices to model these conditional on age only. Since the costs of osteoarthritis obviously depend solely on age, they do not need to be corrected for postponement of costs in the last year of life.

In terms of the theoretical (although perhaps not very practically useful) definition of unrelated costs (as first put forward by Garber and Phelps, 1997), i.e. conditional independence of costs, in the above example the costs of cancer are related (i.e. conditionally dependent) because they do not depend on age but on time to death. Furthermore, the fact that the costs of osteoarthritis increase with age does not imply that they are dependent. The costs of osteoarthritis conditional on reaching a particular age are, in fact, independent of the intervention targeted at cancer. Therefore, they are conditionally independent. More generally, if an intervention extends life, all costs that fully depend on time to death are postponed and, theoretically, can be labelled related. Consequently, the costs that depend exclusively on age can be called unrelated. In the above example, conveniently, the distinction between related and unrelated *costs* matches with the distinction between related and unrelated *diseases*. In reality, however, costs of specific diseases do not depend exclusively on age or time to death, which complicates the separation of related and unrelated costs considerably. For example, costs of cancer in life years gained could include costs of a screening program on cancer that everybody in the population at that age would receive (implying conditional independence).

This paper elaborates on the issue how to include cost in life years gained in common practical cost effectiveness analysis and discusses how ICERs can be adjusted for postponement of the costs in the last year of life if costs of related diseases are already taken into account in the basic economic evaluation. It therefore combines the theoretical literature in this area with the practice of economic evaluations. The structure of the paper is as follows. First, the following section sets out a theoretical framework in which we confront the theoretical debate on unrelated medical care with the so-called ‘red herring’ claim and the practice of economic evaluations in which costs of related diseases are included. Then, using the

example of smoking cessation, we demonstrate the similarities between the ‘red herring’ approach and the disease-specific approach. The paper concludes with a discussion about the proper way to account for medical costs in life years gained in economic evaluations. In our paper, a health care perspective is taken. However, for a societal perspective, the reasoning is completely analogous.

2. THEORETICAL FRAMEWORK

In this section, we will try to reconcile the practice of economic evaluation with the empirical findings on the health care costs of ageing under the now more broadly accepted assumption (Rappange *et al.*, 2008) that both related and unrelated medical costs should be included. To do this, we will use the example of an individual, whose death is postponed if he receives intervention y instead of intervention x at age q . After intervention x this individual will die at age v and after intervention y this person dies at age w . The intervention y results in ‘added’ years that equal w minus v (see Figure 1).

Taking a health care perspective, excluding all costs but those falling under the health care budget, an ICER of intervention y compared with intervention x consistent with maximization of health gains from a given health care budget can then be written as:

$$\text{ICER} = \frac{[oc(y) + lhc(y)] - [oc(x) + lhc(x)]}{\text{QALYs}(y) - \text{QALYs}(x)}$$

Here, for simplicity, it is assumed that costs of the intervention oc (e.g. costs of vaccines, nicotine gum or surgery with $oc(y)$ and $oc(x)$ denoting the intervention costs of intervention y and x respectively) can be separated from all other lifetime health care costs lhc (with $lhc(x)$ and $lhc(y)$ denoting the lifetime health care costs for intervention x and y respectively). For the remainder of this paper, we will focus on the estimation of incremental lifetime health care costs lhc and the implications thereof for the ICER.

The simplest way to estimate lifetime health care costs is to model total health care costs as a function of age only. If health care costs depend solely on age, costs in ‘normal’ years ($v-q$) are identical for intervention y and x and incremental lifetime health care costs are equal to:

$$\begin{aligned} lhc(x) &= \sum_{i=q}^v ac(i) \\ lhc(y) &= \sum_{i=q}^w ac(i) \\ \Delta lhc &= \sum_{i=q}^w ac(i) - \sum_{i=q}^v ac(i) = \sum_{i=v+1}^w ac(i) \end{aligned} \quad (1)$$

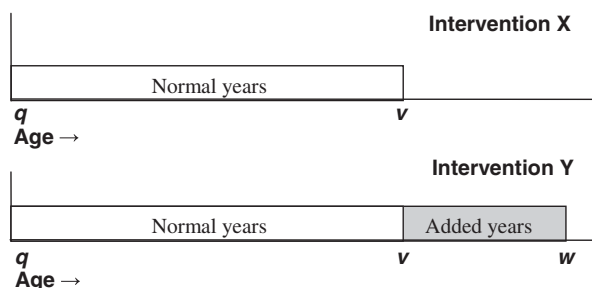


Figure 1. Life years under interventions x and y

with $ac(i)$ the average health care expenditure at age i . This is the approach as perceived by Gandjour and Lauterbach to be current practice in the economic evaluation of preventive interventions. However, if the costs differ whether one survives or dies at a particular age, and given that the costs in the last year of life of year are higher, the story becomes somewhat more complicated:

$$\begin{aligned}
 lhc(x) &= \sum_{i=q}^{v-1} sc(i) + dc(v) \\
 lhc(y) &= \sum_{i=q}^{w-1} sc(i) + dc(w) \\
 \Delta lhc &= \sum_{i=v}^{w-1} sc(i) - dc(v) + dc(w)
 \end{aligned} \tag{2}$$

where $dc(i)$ denotes costs in the last year of life i and $sc(i)$ denotes health care costs during all other years. By definition under intervention y there are no costs in the last year of life during ‘normal’ years (the years lived under both interventions v – q), because this person dies at a later age (w). Furthermore, the costs in normal years are lower under intervention y than intervention x since it does not contain the expensive last year of life anymore: $\sum_{i=q}^{v-1} sc(i) + dc(v) > \sum_{i=q}^v sc(i)$. Thus, by explicitly modeling the last year of life an intervention first results in savings during ‘normal years’. However, after normal years, one incurs extra costs in ‘added years’: $\sum_{i=v+1}^{w-1} sc(i) + dc(w)$. The difference between modelling costs exclusively depending on age and modelling costs also depending on the last year of life was the situation addressed by Gandjour and Lauterbach. Since, in general, health care costs increase exponentially at old age, on balance, modelling costs exclusively conditional on age results in an overestimation of incremental health care costs. However, as we will argue, in most economic evaluations, costs are modelled differently, and adjusting ICERs is not as straightforward as seems to be suggested by Gandjour and Lauterbach.

Usually in economic evaluations it is not the costs that are disentangled into a related and an unrelated component, but the diseases that are categorised as related or not. Related diseases are defined as the diseases at which the intervention investigated is targeted (Gold *et al.*, 1996) and all other diseases are defined as unrelated to the intervention. As noted before, this definition of related and unrelated does not necessarily adhere to the strict definition of conditional dependence and independence. Using this framework, lhc is the sum of related diseases and unrelated diseases and we can denote the following:

$$\begin{aligned}
 lhc(x) &= \sum_{i=q}^v \sum_{e=1}^r rc(i, e|x) + \sum_{i=q}^v \sum_{f=1}^n uc(i, f|x) \\
 lhc(y) &= \sum_{i=q}^w \sum_{e=1}^r rc(i, e|y) + \sum_{i=q}^w \sum_{f=1}^n uc(i, f|y) \\
 \Delta lhc &= \sum_{i=q}^w \sum_{e=1}^r \{rc(i, e|y) - rc(i, e|x)\} + \sum_{i=q}^w \sum_{f=1}^n \{uc(i, f|y) - uc(i, f|x)\}
 \end{aligned} \tag{3}$$

where $rc(i, e|x)$ denotes the costs at age i of related disease e under intervention x , and $uc(i, f|x)$ denotes the costs of unrelated disease f at age i under intervention x . If costs of unrelated diseases are truly independent, unrelated medical costs should be equal in normal years for interventions

y and x : $\sum_{i=q}^v \sum_{f=1}^n uc(i, f|x) = \sum_{i=q}^v \sum_{f=1}^n uc(i, f|y)$ resulting in:

$$\Delta lhc = \sum_{i=q}^w \sum_{e=1}^r \{rc(i, e|y) - rc(i, e|x)\} + \sum_{i=v+1}^w \sum_{f=1}^n uc(i, f|y).$$

The common practice in economic evaluation seems to be to include $\sum_{i=q}^v \sum_{e=1}^r rc(i, e|x)$, $\sum_{i=q}^v \sum_{e=1}^r rc(i, e|y)$ and sometimes $\sum_{i=v+1}^w \sum_{e=1}^r rc(i, e|y)$ resulting in:

$$\Delta lhc = \sum_{i=q}^w \sum_{e=1}^r \{rc(i, e|y) - rc(i, e|x)\} \quad (4)$$

If intervention y postpones or avoids disease, the costs of related diseases in normally lived life years under intervention y are usually lower compared to those in intervention x : $\sum_{i=q}^v \sum_{e=1}^r rc(i, e|y) < \sum_{i=q}^v \sum_{e=1}^r rc(i, e|x)$. Then, in added years, there are the costs of related diseases: $\sum_{i=v+1}^w \sum_{e=1}^r rc(i, e|y) \geq 0$. Moreover, since y is prolonging life and unrelated diseases normally will occur, $\sum_{i=v+1}^w \sum_{f=1}^n uc(i, f|y)$ is positive and therefore, ignoring this term results in an underestimate of the ICER, *ceteris paribus*.

Modelling health care costs as a function of age and time to death has been the primary tool in projections of future health care costs while modelling costs conditional on disease status is used within health economic evaluations. However, these different approaches can be put into a common framework (see Figure 2).

In Figure 2 health care costs are assumed to be a consequence of disease. This implies that the relation between proximity to death and health care costs is driven by the relation between the costs of individual diseases and proximity to death. As can be seen from Figure 2, if an intervention postpones death by postponement or avoidance of a disease or improved disease prognosis, this will result in postponement of costs. This can be modelled either conditional on disease status or conditional on time to death.

Comparing Equations (2) and (3) demonstrates that for a life-saving intervention, both the red herring approach and the disease-specific approach results in savings in 'normal' years and extra costs in 'added' years.

Now let us turn to the question as to how to adjust an ICER that already includes the lifetime costs of related diseases (as in Equation (4)). Straightforward addition of all costs stratified by survivors and decedents to a standard ICER that includes costs of related diseases results in double counting of savings in normal years $\{sc(v) - dc(v)\} + \sum_{i=q}^v \sum_{e=1}^r \{rc(i, e|y) - rc(i, e|x)\}$ and double counting of costs in added life years $\{dc(w) + \sum_{i=v+1}^{w-1} sc(i)\} + \sum_{i=v+1}^w \sum_{e=1}^r rc(i, e|y)$ resulting in the following expression:

$$\Delta lhc = \{sc(v) - dc(v)\} + \sum_{i=q}^v \sum_{e=1}^r \{rc(i, e|y) - rc(i, e|x)\} + \{dc(w) + \sum_{i=v+1}^{w-1} sc(i)\} + \sum_{i=v+1}^w \sum_{e=1}^r rc(i, e|y) \quad (5)$$

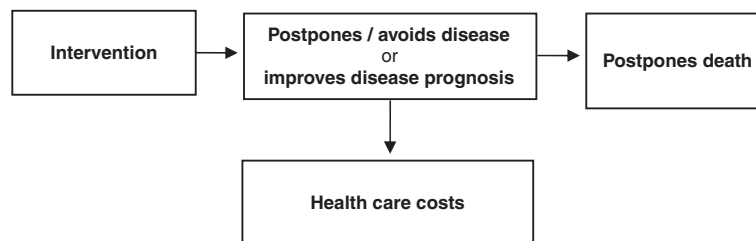


Figure 2. Relation between intervention, mortality and health care costs

Subsequently, the question is how to adjust Δlhc estimated as in Equation (4) for the costs of unrelated diseases. Explicit modelling of all unrelated diseases is an unpractical approach. A more practical approach is to use total health care expenditure as a starting point. Then, first, costs of related diseases can be subtracted from total health care costs. Second, it should be investigated whether the relation between time to death and health care costs is altered after the costs of related diseases are excluded. This will demonstrate the extent to which the related illnesses have captured the postponement effect and, consequently, to what extent this postponement effect is already captured in the estimations. If related diseases include some major causes of death, the relation between unrelated diseases and time to death probably is weaker than the relation between total costs and time to death. The question is whether the relation is still strong enough to warrant correction for the last year of life. Note that this problem arises because of the fact that although, in theory, *unrelated costs* should depend solely on age, this will not as a rule be the case for *costs of unrelated diseases*. *Unrelated costs* is a different concept than that of the *costs of unrelated diseases*, implying that normally not all death-related costs are included in the costs of related diseases.

In the next section we highlight the practical implications of these different approaches using the example of smoking cessation.

3. CASE STUDY: SMOKING CESSATION

3.1 Methods

This section demonstrates the effects of using different methodologies to calculate lifetime health care costs by the example of a smoking cessation intervention. We show that the disease-specific approach and the red herring approach both capture the same postponement mechanism. The intervention evaluated is increased implementation of a smoking cessation intervention, Minimal counselling by a GP and/or a GP-assistant in combination with nicotine replacement therapy in Dutch adult smokers (Silagy *et al.*, 2002). Details of how we modelled this intervention were published previously (Feenstra *et al.*, 2005). In short, a current practice scenario (CP) was defined as the mixture of all current initiatives to stop smoking and willpower alone. In an intervention scenario, during 1 year, 25% of all smokers between 60 and 64 were given minimal counselling with nicotine replacement therapy and showed increased cessation rates. To estimate QALYs and health care costs for the current practice and intervention scenario, the RIVM Chronic Disease Model (CDM) was used (see Appendix) (Hoogenveen *et al.*, *in press*; van Baal *et al.*, 2006; Hoogenveen *et al.*, 2008). ICERs were then calculated for different values of the discount rate as advised by Dutch, British and American guidelines (CVZ, 2005; Claxton *et al.*, 2006; Gold *et al.*, 1996).

Estimates of lifetime health care costs using the CDM were based on the data of the Costs of Illness in the Netherlands study (Slobbe *et al.*, 2006; van Baal *et al.*, 2008, 2007b). By partitioning the costs of illness data in different ways (see Appendix) we could estimate the following five ICERs (for ease of notation we have omitted summation indices in the ICERs, e.g. $rc(x)$ denotes the lifetime health costs of all related disease under intervention x):

1. ICER 1 assumes that lifetime health care costs of all diseases are taken into account but that they are modelled using only age as explanatory variable (as in Equation (1)):

$$ICER1 = \frac{[oc(y)+ac(y)] - [oc(x)+ac(x)]}{QALYs(y) - QALYs(x)}$$

Gandjour and Lauterbach assumed this ICER to be used in most economic evaluations of preventive care.

2. ICER2 also takes total health care expenditure into account, but now models the expensive last year of life explicitly as in Equation (2):

$$\text{ICER2} = \frac{[oc(y) + sc(y) + dc(y)] - [oc(x) + sc(x) + dc(x)]}{\text{QALYs}(y) - \text{QALYs}(x)}$$

This ratio was proposed by Gandjour and Lauterbach as an improvement of ICER1. This ratio takes into account the postponement of health care costs.

3. ICER3 is most often seen in economic evaluation and includes costs of related diseases in normal as well as added life years as in Equation (4). Costs of unrelated diseases are not included and costs of related diseases are modelled conditional on disease status:

$$\text{ICER3} = \frac{[oc(y) + rc(y)] - [oc(x) + rc(x)]}{\text{QALYs}(y) - \text{QALYs}(x)}$$

This ratio accounts for postponement of the costs of related diseases, but ignores costs of unrelated diseases.

4. ICER4 completes ICER3 by adding the costs of unrelated diseases as in Equation (3). The costs of remaining unrelated diseases are here assumed to depend on age only (see Appendix):

$$\text{ICER4} = \frac{[oc(y) + rc(y) + uc(y)] - [oc(x) + rc(x) + uc(x)]}{\text{QALYs}(y) - \text{QALYs}(x)}$$

5. ICER5 constitutes a correction of ICER3 using costs of survivors and decedents but ignoring the fact that costs of related diseases are already included in ICER3 (as in Equation (5)):

$$\text{ICER5} = \frac{[oc(y) + rc(y) + sc(y) + dc(y)] - [oc(x) + rc(x) + sc(x) + dc(x)]}{\text{QALYs}(y) - \text{QALYs}(x)}$$

ICER5 involves double counting of savings in normal years and extra costs in added years.

Based on our theoretical framework, we would expect that ICER1 is highest since it ignores savings in normal years and that ICER3 is lowest since only the costs of related diseases are taken into account in which we expect savings. We expected that the values for ICER2 and ICER4 would be in close range since both capture the same postponement mechanism and would result first in savings and then in extra costs. We did not have an *a priori* hypothesis whether ICER5 would be lower or higher than ICER4.

3.2 Results

Figure 3 displays differences in health care costs over time due to the smoking cessation intervention.

Figure 3 illustrates that if lifetime health care costs are estimated as a function of age only, prevention does not result in savings in the short run and thus ignores the postponement component of prevention. The differences in the costs of survivors and the costs of unrelated disease follow a similar pattern as they also depend on age exclusively. More importantly, it is observable that both the costs of related diseases and the costs in the last year of life are postponed by the intervention. However, if costs are calculated conditional on disease status, short run savings are higher while long run additional costs are lower. A possible explanation for this phenomenon might be that modelling costs conditional on disease status allows for differential effects of interventions on health care costs, for instance, that expensive causes of death are replaced by cheaper causes of death. In case of smoking, expensive causes of death such as lung cancer and COPD are replaced by cheaper causes of death such as coronary heart

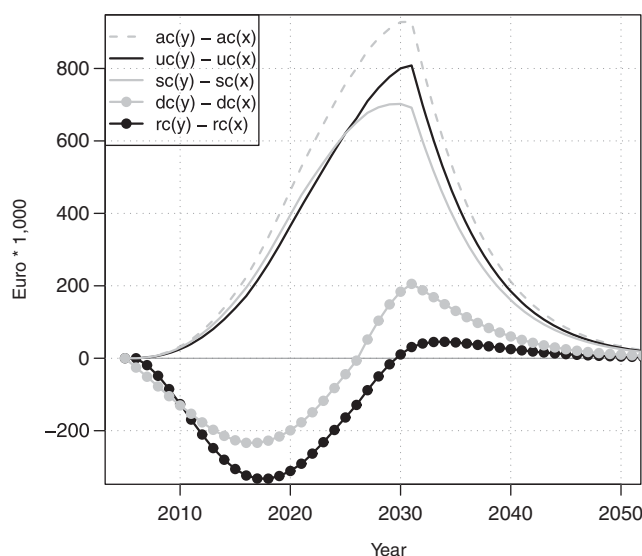


Figure 3. Difference in health care costs over time (excluding costs of the smoking cessation intervention) due to smoking cessation intervention (discount rate 4%)

Table I. Incremental cost effectiveness ratios (ICER) expressed in € per QALY gained of smoking cessation intervention for different discount rates

	Dutch guidelines	US guidelines	UK guidelines
Discount rate costs	4%	3%	3.5%
Discount rate effects	1.5%	3%	3.5%
ICER1 (simple approach: age-related costs only)	14 200	22 000	22 200
ICER2 (simple approach accounting for time to death)	11 900	18 500	18 600
ICER3 (standard approach: costs of related diseases)	2600	3200	3600
ICER4 (standard approach accounting for unrelated diseases)	10 400	16 100	16 200
ICER5 (double counting)	9600	15 100	15 100

disease. These more refined mechanisms cannot always be picked up by the proximity to death approach.

Table I gives the different ICERs of the smoking cessation intervention example for discount rates as used in the Netherlands, USA and the UK.

Table I shows that ICER1 is highest and ICER3 is lowest for all values of the discount rate. Moreover, ICER2 and ICER4 produce similar results. ICER5 is lower than ICER2 and ICER4 showing that, on balance, the double counting of savings in normal life years and costs in added years results on balance only in a slight underestimation of the ICER for this specific example.

4. DISCUSSION AND CONCLUSIONS

In this paper, we have discussed the difficulties and different approaches related to the inclusion of costs in life years gained in economic evaluations, combining insights from the theoretical debates and the 'red herring' literature, as well as considering the practice of current economic evaluations. Importantly, cost-effectiveness analyses overstate the cost-effectiveness ratio of life-saving interventions if they do not explicitly model the costs of the last year of life, which is postponed. However, we showed that in economic

evaluations already a part of this postponement mechanism is taken into account if studies include lifetime cost differences of so-called related diseases. If an intervention extends life, some costs of related diseases usually are avoided altogether, while others are postponed. This mechanism is already captured by explicit modelling of these diseases and their costs. Adding costs of survivors and descendents using a red herring approach may result in double counting of both the savings in normal live years and the costs in life years gained. Since both savings as well as costs may be double-counted, these both effects may, to some – unknown and probably intervention specific – extent, cancel out. In our example this resulted, on balance, only in a slight underestimation of the ICER. However, it is important to be aware of these two different approaches, since mixing them may result in conceptually wrong cost-effectiveness ratios and over-correction. Since the differences and therefore the misrepresentation of true cost-effectiveness may be more pronounced in other cases, this issue ultimately is also important in the context of health policy and decision making. Indeed, ignoring or misrepresenting the here discussed costs and savings may result in non-optimal decisions when they push an ICER unduly above or below the relevant threshold in a specific jurisdiction. Hence, clarity about how these costs were included in an analysis is warranted.

If we apply the theoretical definition of conditional independence, unrelated medical costs in life years gained should be independent of time to death. However, in economic evaluations typically not the *costs* are disentangled into a related and an unrelated component, but rather the *diseases*. The two are, however, clearly not the same, implying that many practical applications of economic evaluations include wrong estimates of ‘related costs’. Thus, in practice not all costs that are related are taken into account in economic evaluations since only costs of the diseases at which the intervention is targeted are included. The question then becomes how to account for the costs of unrelated diseases in life years gained. Are their costs dependent on proximity to death too? We hypothesise that the relation between time to death and health care costs may differ per disease. Furthermore, we hypothesise that the relation between time to death and health care costs is strongest for diseases that increase mortality rates. This implies that if related diseases include some major causes of death (like in our smoking example), the relation between unrelated diseases and time to death is (much) weaker than the relation between total costs and time to death and an additional correction for the last year of life might be superfluous. Using the example of smoking cessation we showed that if unrelated diseases were modelled conditional on age only, a proximity to death methodology produced similar results as a disease-specific approach. However, for other analyses that included a more limited set of related diseases, it might still be important to correct for time to death to estimate the costs of unrelated diseases. In theory, an attractive option for updating economic evaluations would be to combine the two approaches, which requires assessing the effect of age and time to death on health expenditures for each *disease* separately. This crucially depends on the availability of rather detailed longitudinal data, including disease status measured repeatedly. In the absence of these disease-specific ‘red herrings’, calculated in a systematic way, a more opportunistic and feasible approach seems to be to deliberately choose one of the two methods set out above.

We argue that the separation of costs into a related and unrelated component is unnecessary and creates more problems than it solves. This is especially the case given the current state of affairs in economic evaluations to include the *costs of related diseases* instead of *related costs*. If one wishes to update these common ICERS, the discussed problems may occur. If all lifetime health care costs are included in an economic evaluation, the distinction between related and unrelated diseases becomes irrelevant, which opens up alternative ways to estimate health care costs. Moreover, since a large part of lifetime health care expenditure depends on time to death (Zweifel *et al.*, 1999; Polder *et al.*, 2006) this implies that probably more costs are then labelled ‘related’ than currently assumed in most cost effectiveness analyses, which usually only include the costs of diseases that are treated with the intervention. Modelling costs exclusively conditional on age and time to death seems to have most value for economic evaluations that track costs and effects over the follow-up period and use modelling to extrapolate lifelong health gains. In those circumstances, no effort is made to distinguish between the effects of the intervention on the costs of different diseases. If survival is modelled for both the control

and the treatment group beyond follow-up, these survival curves simply can be coupled to age-specific costs of decedents and survivors. While this approach is simple to develop and can be applied similarly across a range of interventions, it does have an important limitation. In the proximity to death approach, the relationship between age, mortality and health care costs is assumed fixed and does not discriminate between interventions that differ in their effect on related diseases. Using a disease-specific model does allow expensive causes of death to be replaced by cheaper causes of death and vice versa. If these types of mechanisms are expected to be influential, a disease-specific approach is preferred and disease-specific estimates of the relationship between age, mortality and health care costs would be required.

Note that this paper has focused solely on indirect health care costs and ignored indirect non-medical costs, in line with most of the 'red herring' literature. While it is important to further the debates and practice in the area of indirect medical costs, we wish to stress that non-medical costs might, for some applications, be an even more important cost category. In that area, there is still much theoretical discussion (Meltzer, 1997; Nyman, 2004; Lee, 2008; Feenstra *et al.*, 2008) regarding whether these costs should indeed be included in an economic evaluation, which obviously also relates to the perspective chosen for the evaluation. As yet, only few empirical studies (Meltzer, 1997 being a notable exception) have attempted to address this topic more systematically, but we would encourage a broadening of the scope of current debates to include these costs as well.

Concluding, it is clear that if unrelated costs in life years gained are to be included in economic evaluations, the question of *how* they should be included is not straightforwardly answered. Researchers obviously should be aware of postponement mechanisms in the costs of related and unrelated diseases and as such should carefully choose and justify their method of inclusion of costs in life years gained to avoid double counting or overstatement of ICERs. With the growing consensus on the inclusion of unrelated costs in life years gained, it is likely that their inclusion will be facilitated through new research and standardisation of methodology in the coming years. In the end, this will result in better estimates of cost-effectiveness of interventions, and as such, may contribute to the ultimate aim, i.e. an optimal allocation of scarce resources in the health care sector.

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APPENDIX A

To estimate QALYs and health care costs for the current practice and intervention scenario, the RIVM Chronic Disease Model (CDM) was used (Hoogenveen *et al.*, *in press*; van Baal *et al.*, 2006; Hoogenveen *et al.*, 2008). The CDM is a tool to describe the morbidity and mortality effects of risk factors for chronic diseases, including smoking and overweight and has been used for projections of risk factor and disease prevalence and cost effectiveness analysis (van Baal *et al.*, 2006, 2007a; Feenstra *et al.*, 2001, 2005; Struijs *et al.*, 2005; Jacobs-van der Bruggen *et al.*, 2007). The model describes the life course of cohorts in terms of changes between risk factor classes and changes between disease states over time. The model allows for co-morbidity and includes data on the most important chronic diseases

and their risk factors. Risk factors and diseases are linked through relative risks on disease incidence with the relative risks of former smokers on 14 smoking-related disease declining from the risk of a smoker to that of a never smoker as a function of time since cessation. Restart rates of former smokers are also a function of the time since smoking cessation. Since the presence of a disease increases mortality rates, risk factor levels influence mortality through disease incidence.

A.1. Calculating health care costs with the RIVM chronic disease model (CDM)

To estimate health care costs for different scenarios with the CDM data of the Costs of Illness (COI) in the Netherlands study were used (Slobbe *et al.*, 2006). In that study the total direct health care costs in the Netherlands of 2003 are uniquely attributed to disease categories specified by gender and age classes. For the current study the COI data were partitioned in different ways to estimate lifetime health care costs in different manners.

A.1.1. Partitioning costs to age. As a first step, age and sex-specific average health care costs per person are calculated using COI data in the following manner (note: all input parameters and model calculations are age and gender specific, but for notational purposes we have omitted age and gender indices):

$$ac = \frac{\sum_d COI(d)}{pop}$$

where ac is the average health care costs per person, $COI(d)$ is the health care costs for disease d in 2003 and pop is the population size in the Netherlands in 2003.

Age and sex-specific health care costs defined as sum of health care costs over all diseases are divided by population numbers to obtain average health care costs per person. Average health care costs per person are multiplied with survivor numbers calculated with the CDM to calculate lifetime health care costs:

$$ac(x) = \sum_{t=1}^m (1+dr)^{-(t-1)} * s(t|x) * ac$$

where $s(t|x)$ is the number of survivors year t estimated with the CDM under intervention x , m is the time horizon and dr is the discount rate.

A.1.2. Partitioning costs to age stratified to survivors and decedents. To estimate age and sex-specific health care costs for survivors, COI data are partitioned in the following manner:

$$sc = \frac{ac}{1+(z-1)*k}$$

$$dc = sc * z$$

where sc is the average health care costs survivors, z is the ratio of costs per year (decedents/survivors), k is the mortality rate in 2003, and dc is the average health care costs decedents.

Costs for survivors and decedents are calculated using mortality rates for 2003 in the Netherlands (Statistics Netherlands, 2006) and the ratio between health care costs for those dying at a particular age and those surviving at that age. This ratio has been estimated for the Netherlands (Polder *et al.*, 2006). Age and sex-specific average costs for survivors then serve as input for the model to calculate lifetime health care costs conditional on survivor numbers and numbers of decedents within a year period:

$$sc(x) = \sum_{t=1}^t (1+dr)^{-(t-1)} * s(t|x) * sc$$

$$dc(x) = \sum_{t=1}^t (1+dr)^{-(t-1)} * [s(t|x) - s(t-1|x)] * dc$$

A.1.3. Partitioning costs to related and unrelated diseases. To assign the COI data that give total costs per related disease to individual patients, total costs per disease were divided by the disease prevalence numbers for 2003.

$$rc(e) = \frac{COI(e)}{p(e)}$$

where $rc(e)$ is the costs per year per patient for related disease e , $COI(e)$ total costs related disease e in 2003, $p(e)$ is the prevalence number of related disease e in 2003.

Given the estimated costs per patient per disease per year we can write the lifetime health care costs of related diseases as a function of disease prevalence numbers estimated with the CDM:

$$rc(x) = \sum_{t=1}^m (1+dr)^{-(t-1)*} \sum_{e=1}^r p(e, t|x) * rc(e)$$

where $p(e, t)$ is the prevalence number of related disease e in year t estimated with the CDM.

We did not have data to estimate the relationship between proximity to death and the costs of unrelated diseases. The model we used for the example explicitly modelled 14 smoking-related diseases (e.g. coronary heart disease, stroke, COPD and lung cancer) that account for more than two thirds of mortality in the Netherlands. In accordance with our theoretical framework, we hypothesised that the relation between health care costs and proximity to death would be absent if the costs of related diseases are excluded. Hence, we assumed that the costs of unrelated diseases were not related to proximity to death and only depend on age. To calculate health care costs for all unrelated diseases, the numbers of survivors were multiplied by age and sex-specific average health care costs for other diseases (i.e. costs remaining when costs of smoking related diseases are subtracted from total costs):

$$uc = ac - \frac{\sum_{e=1}^r COI(e)}{pop}$$

where uc is the annual health care costs per person for all unrelated diseases.

We estimated the average health care costs of all other diseases and multiplied by the number of survivors:

$$uc(x) = \sum_{t=1}^t (1+dr)^{-(t-1)*} s(t|x) * uc$$

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